

## REMARKS

The Applicant requests that the Examiner enter the amendment prior to examining the application. This amendment is intended as a full and complete response to the Office Action dated June 29, 2005. A notice of appeal was timely filed on September 29, 2005. This amendment and a request for continued examination (RCE) are timely, as they are being filed with a one month extension of time to and including December 29, 2005. Please reconsider the claims pending in the application for reasons discussed below.

Claims 44, 47, 48, and 56-61 remain pending in the application and are shown above. Claims 49-55 have been canceled by Applicants. Claims 44, 47, 48, and 56-61 are rejected. Reconsideration of the rejected claims is requested for reasons presented below.

Claim 44 has been amended to more clearly illustrate the claimed subject matter. As amended, claim 44 describes an isolated nucleic acid that includes a first RNA sequence and a second RNA sequence that are transcription products of a construct comprising a transcription terminator sequence that is operable in a mammalian cell. Applicants submit that the changes made herein do not introduce new matter.

In the Final Office Action dated June 29, 2005, the Examiner asserted that the claims were denied benefit of the parent application because the parent applications do not contain support for an RNA sequence limited to about 20-100 nucleotides in length. Applicants note that the instant application is a continuation of United States Patent Application Serial No. 10/646,070, which is a continuation of United States Patent Application Serial No. 09/646,807, which is a continuation of PCT/AU99/00195, which was filed on March 19, 1999. Page 8, line 21 of PCT/AU99/00195 provides support for an RNA sequence having a length of "at least 20-100 nucleotides." Applicants submit that the phrase "at least 20 and up to 100 nucleotides" is supported by the phrase "at least 20-100 nucleotides" and is a clear and reasonable interpretation of the phrase "at least 20-100 nucleotides." Applicants have amended claim 44 to recite "at least 20 and up to 100 nucleotides." Thus, Applicants submit that the claims are entitled to at least the March 19, 1999 filing date of the priority application PCT/AU99/00195.

The Examiner has indicated in the Advisory Action dated September 14, 2005 that the Information Disclosure Statement filed on April 29, 2005 has not been considered because it did not include a PTO/SB/08 or PTO-1449 form. Applicants are submitting a replacement Information Disclosure Statement that includes the four references submitted with the Information Disclosure Statement filed on April 29, 2005 and a PTO/SB/08 form.

The oath or declaration is objected to. The Examiner states that the declaration as filed is defective because it does not reflect that the application is a continuation-in-part. The Examiner asserts that the application is a continuation-in-part because the claims in the preliminary amendment filed on April 8, 2004 were drawn to subject matter that he did not believe was supported by the original disclosure. Applicants note that the claims have been amended to remove the subject matter identified by the Examiner as new matter. As discussed above, amended claim 44 is entitled to priority to PCT/AU99/00195, which is the subject of declaration. Applicants respectfully request withdrawal of the objection to the declaration.

The specification is objected to for failing to provide proper antecedent basis for claims 49-55. Applicants have canceled claims 49-55. Applicants submit that the changes made herein do not introduce new matter. Applicants respectfully request withdrawal of the objection to the specification.

Claims 44, 47-48, and 56-61 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that specification does not reasonably provide enablement for the broad scope of any isolated nucleic acid molecule capable of post-transcriptionally repressing, delaying, or otherwise reducing expression of a target gene in a mammalian cell. The Examiner further states that the specification does not enable making and using the invention commensurate in scope with the claims. Applicants respectfully traverse the rejection.

The Examiner is relying on two assertions to support his finding that the scope of the claims is not enabled: 1. that RNAi in mammalian cells using dsRNA greater than 30 nucleotides is difficult because of potential side effects, such as an interferon response and 2. obtaining an RNAi response using a siRNA targeted to any given region of any given gene is unpredictable. Regarding the Examiner's concerns about

using longer dsRNA, Applicants note that longer dsRNA has been used to achieve RNAi, as shown in Park, et al. *Nucleic Acids Res.* 2002 Nov 15;30(22):4830-5, Yamamoto, et al., *Microbiol Immunol.* 2002 46(11): 809-817, Park, et al., *Nucleic Acids Res Suppl.* 2001;(1):219-20, and Gitlin, et al., *J Virol.* 2005 Jan;79(2):1027-35, which are submitted herewith on the accompanying Information Disclosure Statement. Furthermore, literature in the field indicates that it is unclear whether long dsRNA triggers an interferon response in mammalian cells (See Robbins, et al. *Nature Medicine* March 2005 Vol 11(3): 250-251, which is submitted herewith on the accompanying Information Disclosure Statement). In particular, Applicants submit that it is unclear whether long dsRNA that is expressed inside a cell, as claimed in the instant application, rather than introduced from outside of the cell, triggers an interferon response.

Regarding the Examiner's concerns that obtaining an RNAi response using a siRNA targeted to any given region of any given gene may be unpredictable, Applicants submits that the Examiner is placing an impossible burden on Applicant to show a 100% success rate in the field of molecular biology. It is routine, not undue, experimentation in molecular biology to choose a target region of a gene, create multiple constructs based on the target region, and screen for successful candidates and choose those constructs showing the desired result for further analysis or use. Even routine molecular biology procedures, such as generating subclones or monoclonal antibodies, require generating multiple candidates that are screened. Applicants respectfully submit that given the detailed description of the constructs that are provided in the specification (and which are easily usable with target genes other than those described in the examples) and the high level of skill in the art, one of ordinary skill in the art would be able to perform the invention as claimed with an expected but not undue amount of experimentation.

Claims 44, 47-48, and 56-61 stand rejected under 35 U.S.C. § 102(a) as being anticipated by *Harboth, et al.* (publicly available 12 May 2003) *Antisense Nucl. Acid Drug Devel.* 13:83-105. Applicants respectfully submit that while *Harboth, et al.* describes synthetic siRNAs (p. 86-87), *Harboth, et al.* does not teach or suggest a siRNA that is an isolated nucleic acid comprising a first RNA sequence and a second

RNA sequence, wherein the first RNA sequence and the second RNA sequence are transcription products of a construct comprising a transcription terminator sequence that is operable in a mammalian cell. Furthermore, as discussed above, the pending claims are entitled to at least the March 19, 1999 filing date of the priority application PCT/AU99/00195. Thus, *Harboth, et al.* should not be used as prior art against the pending claims. Applicants respectfully request withdrawal of the rejection of claims 44, 47-48, and 56-61.

Claims 44, 47, and 56-61 stand rejected under 35 U.S.C. § 102(b) as being anticipated by *McManus, et al.*, (2002) *RNA* 8:842-850. *McManus, et al.* describes hairpin RNAs that may be transcribed from DNA constructs. *McManus, et al.* teaches that termination of transcription of the constructs occurs at the 3' end of the hairpin itself. *McManus, et al.* (bottom of p. 847 to top of p. 848) indicates that the terminating region is transcribed ("transcription termination occurs at a stretch of 5-thymidine residues at the 3' end of the hairpin encoding U's in the RNA; Fig. 6A"). *McManus, et al.* does not teach or suggest using a construct comprising a separate, non-transcribed transcription terminator sequence. Furthermore, as discussed above, the pending claims are entitled to at least the March 19, 1999 filing date of the priority application PCT/AU99/00195. Thus, *McManus, et al.* should not be used as prior art against the pending claims. Applicants respectfully request withdrawal of the rejection of claims 44, 47, and 56-61.

Claims 44, 47, 56, 57, 60, and 61 stand rejected under 35 U.S.C. § 102(b) as being anticipated by *Elbashir, et al.* (2002) *Methods* 26:199-213. Applicants respectfully submit that while *Elbashir, et al.* describes synthetic siRNAs (p. 202-203), *Elbashir, et al.* does not teach or suggest a siRNA that is an isolated nucleic acid comprising a first RNA sequence and a second RNA sequence, wherein the first RNA sequence and the second RNA sequence are transcription products of a construct comprising a transcription terminator sequence that is operable in a mammalian cell. Furthermore, as discussed above, the pending claims are entitled to at least the March 19, 1999 filing date of the priority application PCT/AU99/00195. Thus, *Elbashir, et al.* should not be used as prior art against the pending claims. Applicants respectfully request withdrawal of the rejection of claims 44, 47, 56, 57, 60, and 61.

Claims 44, 47, 48, and 58-61 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner asserts that the limitation "greater than 20-100 nucleotides in length" in claim 44 is indefinite. As discussed above, Applicants have amended claim 44 to clearly recite "at least 20 and up to 100 nucleotides in length." Applicants respectfully request withdrawal of the rejection of claims 44, 47, 48, and 58-61.

In conclusion, the references cited by the Examiner, alone or in combination, do not teach, show, or suggest the invention as claimed.

Having addressed all issues set out in the office action, Applicants respectfully submit that the claims are in condition for allowance and respectfully request that the claims be allowed.

Respectfully submitted,

Mireille C. Perret  
Mireille C. Perret  
Registration No. 47,854  
PATTERSON & SHERIDAN, L.L.P.  
3040 Post Oak Blvd. Suite 1500  
Houston, TX 77056  
Telephone: (713) 623-4844  
Facsimile: (713) 623-4846  
Agent for Applicant

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